ORIGINAL RESEARCH

Evaluation of Solvent Efficacy of the *Myrciaria Dubia* (Camu-camu) Essential Oil in Root Canal Re-treatment Procedures: An *In Vitro* Study

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Abstract

Aim: To evaluate the solvent efficacy of an experimental substance based on the *Myrciaria dubia* (camu-camu) essential oil in root canal re-treatment procedures.

Materials and methods: Sixty polylactic acid tubes (PLA) were used and divided into five groups (distilled water, *M. dubia* oil (camu-camu), xylene, orange peel, and eucalyptus oil). In each group, 12 tubes were filled with a temporary restorative material (Coltosol®). The upper and the middle part were filled with gutta-percha. A total of 0.1 mL solvent was added depending on the study group and left for 5 minutes. Once the solvent was placed, the samples were taken to the Instron 3382 machine. The force used to penetrate the spreader into the 5 mm depth was recorded in Newton (N). The Kruskal–Wallis test and Dunn's *post hoc* test were used for multiple comparisons ($p < 0.05$). Statistical analysis was performed using Stata® v.15.0 package.

Results: We found significant statistical differences when comparing all solvents ($p = 0.001$), obtaining 14.02 N for the experimental substance. The results of the superficial dissolution depth and the force used to penetrate the spreader to 5 mm revealed that the *M. dubia* oil (camu-camu) was the solvent that significantly softened the gutta-percha the most ($p < 0.05$). These values were followed by xylene and orange peel oil. We also found that the solvent with the lowest efficacy was eucalyptus oil.

Conclusion: The *M. dubia* (camu-camu) essential oil had more softening power than other solutions in the study.

Clinical significance: The efficacy of the *M. dubia* (camu-camu) essential oil is relevant as it is a nonharmful solvent that would not harm the periapical tissue and would reduce the time of endodontic re-treatments procedures, which is beneficial for patients.

Keywords: Eucalyptus oil, Gutta-percha solvent, *Myrciaria dubia*, Orange peel oil, Xylene.

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Introduction

In some cases, the endodontic treatment performed on teeth fails. In that scenario, the best option is the perform endodontic re-treatment.[1–3] This procedure is among the most complicated in endodontics. Filling and sealing materials used in the previous endodontic treatment (i.e., gutta-percha and cement) must be easily removed through complementary materials (such as an organic solvent) or a heated instrument.[4–7]

Solvent efficacy is a property related to the capacity of the solvent's dissolution, which in this case, it would be the thermoplastic material (gutta-percha). Several studies have used penetration force to determine this efficacy, defined as the capacity to perform a vertical movement when introducing an element inside another.[8,9] This means that the lower the penetration force, the higher the solvent efficacy.

Solvents are substances (solid, liquid, or gas) where the solute is diluted, resulting in a dissolution. Some solvents used are based on natural materials, like orange peel, lime, and eucalyptus. It is proven that essential oils efficiently dissolve the cement used in the obturation of root canals.[10,11] As their main characteristics, they are biocompatible, noncarcinogenic, and nonharmful to human beings.

M. dubia (camu-camu) is a local fruit of the Amazonian region with a high content of ascorbic acid, found in the Plurinational State of Bolivia, Republic of Ecuador, Federative Republic of Brazil, and Peru. The Amazon rainforest has the highest amount of this fruit, mainly in the provinces of Pucallpa and Pebas.[12] A relevant characteristic of this fruit is its high vitamin C concentration in Republic of Ecuador, providing antioxidant, immunomodulator, antiflu, anticarcinogenic, antimicrobial, protective, and cell regeneration properties. It also contains small amounts of iron, calcium, niacin, riboflavin, thiamine, and other phytochemical elements.[13]

It has been shown that natural oils such as eucalyptus, orange peel, lime, grape, and lemon have a high solvent efficacy. The same can be expected with *M. dubia* (camu-camu) oil. In this respect, the D-limonene mineral has been found in the peel and seed of the *M. dubia* (camu-camu) through an atomic absorption technique.[14]

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Therefore, the aim of the present study was to determine the solvent efficacy of an experimental substance based on the *M. dubia* (camu-camu) essential oil compared to distilled water, xylene, orange peel oil, and eucalyptus.

Materials and Methods

The current study was approved by the Research Ethics Committee of Universidad Peruana de Ciencias Aplicadas (UPC) (Lima, Peru) (approval number PI081-19).

Sample Determination

Sixty cylinder-shaped tubes of PLA (5 × 30 mm) were used as test specimens. The tubes were divided into three segments of 10 mm. The bottom segment was filled with a temporary filling material (Coltosol®), the middle segment with gutta-percha (Spident) (10 mm), and the upper segment with the solvent solution. Subsequently, the Instron machine was used to determine the solvent efficacy in N. Specimens that had any fracture or dimensional changes were excluded. Specimens were randomly divided into five groups of 12, and the solvents used for each group were distilled water (Martinotti, Lima, Peru) as a negative control, *M. dubia* (camu-camu), xylene (Xilodent, Proquident, Republic of Colombia) as a positive control, orange peel oil (Maquira, Maringá, Federative Republic of Brazil), and eucalyptus oil (EGEO SRL, Argentina Republic). The formula of comparison of means was used with a 95% confidence level and an 80% power.

Sample Preparation

Temporary filling Placement

For the preparation of the sample, 3 gm of Coltosol® temporary cement (Coltène, Altstätten, Switzerland) was used with the aid of an endodontic plugger [Dentsply Tulsa, Tulsa, Oklahoma, United States of America (USA)] to efficiently compact it in the bottom segment of the tube.

Gutta-percha Obturation

The middle segment of the PLA tube was filled with Spident gutta-percha cones (Spident, Incheon, Republic of Korea) to simulate a filling. This was compacted with the aid of a root canal plugger until no free space inside the tube was seen.

Myrciaria dubia (Camu-camu) Essential Oil Preparation

Steam distillation equipment was used to extract the essential oil. About 60 kg of *M. dubia* (camu-camu) were used, and we chose those with a greenish-red appearance. After approximately 8 hours of distillation, the essential oil was extracted, and any remaining water was removed using anhydrous sodium sulfate. Finally, the pure essential oil was collected in an airtight glass bottle and refrigerated at a temperature below 5°C for better preservation.

A total of 0.1 mL solvent was added to the upper part of the PLA tube and left for 5 minutes.

Solvent Efficacy Measurement

Once the solvent was placed, the samples were taken to the universal testing machine (UTM) (3382 Instron 100 kN, USA) to measure the solvent efficacy through the penetration force (Fig. 1). An accessory instrument was designed to have a 30 mm spacer as an active part, similar to a spreader C, which entered through the filling material. This accessory instrument was moved vertically to the interior of the filling at a speed of 5 mm/minute. In this manner, it was penetrated up to a 5 mm depth into the gutta-percha. The measurement of the force used by the accessory through the gutta-percha was recorded in N through the Instron Bluehill software (Norwood, Massachusetts, USA).

Fig. 1: Evaluation of solvent efficacy through the penetration force using an Instron UTM

Acquisition of Solvents

The solvents used in this study were obtained from commercial dental offices: xylene (Xilodent, Proquident®, Republic of Colombia), orange peel oil (Maquira®, Maringá, Federative Republic of Brazil), eucalyptus oil (EGEO SRL®, Argentina), and distilled water (Martinotti®, Lima, Peru).

Statistical Analysis

Mean, standard deviation (SD), and interquartile range according to the established study groups were calculated. The Kruskal–Wallis test was used to compare between groups, followed by Dunn's *post hoc* test for within comparisons ($p < 0.05$). Statistical analysis was performed with Stata v.15.0 (Stata Corporation, College Station, Texas, USA).

Results

The penetration force values obtained when entering the spreader revealed different values. The *M. dubia* (camu-camu) had the lowest penetration force, meaning that there was a significantly better performance in softening the gutta-percha ($p < 0.05$). The penetration force used to move the spreader was 14.02 N. Table 1 shows the mean and SD values of the force used for the spreader penetration in the distilled water, xylene, orange peel, and eucalyptus oil. These values were 26.49, 18.32, 22.13, and 18.35 N, respectively. There was a statistically significant difference between the xylene and the orange peel oil. Both types of oil soften gutta-percha less compared to *M. dubia* (camu-camu) oil ($p < 0.05$). Eucalyptus oil and distilled water were the least effective solvents for dissolving gutta-percha, as seen in Table 2.

Discussion

Endodontic failures may be mainly caused by bacterial infection, iatrogenic events, and persistent apical or pulpal injuries.[15] Solvents help remove the filling material (gutta-percha) from root canals. These are the first option to soften the thermoplastic material in re-treatment procedures. The methods for gutta-percha removal

Table 1: Evaluation of the solvent efficacy of substances: distilled water, *M. dubia* oil (camu-camu), xylene, orange peel oil, and eucalyptus oil, in root canal filling removal

Group	*Mean (N)* ‡	*SD*	*Median*	*Min*	*Max*	*p-value**
Distilled water (*n* = 12)	26.49[a]	0.003	26.50	26.48	26.50	0.001
M. dubia oil (camu-camu) (*n* = 12)	14.02[b]	0.002	14.02	14.02	14.03	
Xylene (*n* = 12)	18.32[c]	0.002	18.32	18.32	18.33	
Orange peel oil (*n* = 12)	18.35[d]	0.001	18.35	18.35	18.36	
Eucalyptus oil (*n* = 12)	22.13[e]	0.030	22.12	22.12	22.22	

[a, b, c, d, e]Different letters indicate significant statistical differences, *Significant, †Newton

Table 2: Comparison of the solvent efficacy of substances: distilled water, xylene, eucalyptus oil, and orange peel oil with *M. dubia* oil (camu-camu) in root canal filling removal

Group *M. dubia oil (camu-camu) compared to*	*p-value**
Distilled water	0.003
Eucalyptus oil	0.005
Orange peel oil	0.008
Xylene	0.007

*Significant

include ultrasound, heating, and instrumentation with a chemical solution, limes, and rotation. The latter, if often used, can enlarge the root canal and possibly cause a perforation. Therefore, the use of natural solvents is a relevant area for investigation.[16–18]

Different methods are used to determine the solvent efficacy of the gutta-percha, such as the weight difference (the measurement obtained using a calibrated weighing scale to find the initial and final weight upon submersion in the solvent). The Δ (difference) between both weights is interpreted as solvent efficacy.[17] Also, the efficacy may be evaluated through images using X-rays or computed tomography scans, where the remaining filling material is found inside the root canal.[18] For this purpose, two image shots are taken, before and after submersion. Furthermore, another way to determine the efficacy of a solution is with the penetration force. Therefore, an accessory is used and introduced into the filling through vertical movements until it reaches a specific depth. The lesser force required showed higher efficiency of solvent. Research shows that this last method is accurate in measurements with the program used by the Instron UTM.[18,19]

The solutions used in endodontics to soften a filling material when conducting root canal re-treatments may differ in chemicals and natural solutions. According to Galiana, xylene is a toxic and irritating compound for periapical tissues.[17] Among the natural solutions are orange peel oil, grapefruit, mandarin orange, lime, lemon, and eucalyptus. They bring similar results to the chemical solvents without causing harmful effects on human beings. Furthermore, current studies are aimed at promoting the use of natural agents for dentistry. In this study, we used eucalyptus and orange peel oil since they did not cause any harm to the root tissue.[20] In addition, the solvents must dissolve gutta-percha at the surface and reduce filling removal time during the endodontic re-treatment.

The results of this study evidenced that the *M. dubia* (camu-camu) essential oil had a penetration force of 14.02 N. Previous research evaluated the xylene and chloroform efficacy and found their penetration forces at 18.1 and 17.9 N, respectively.[21] Most recent studies use nontoxic solutions like mandarin orange, lemon, grapefruit, and lime. The penetration forces of these are 18.35, 23.11, 18.11, and 23.08 N, respectively.[22] Jantarat et al. also found similar results to the previous study.[19] It may be established that all oils used in this study have softening power. However, the *M. dubia* (camu-camu) solution was the most effective compared to the solutions mentioned above.

Among the active compounds found in *M. dubia* (camu-camu), there is a response in the cell activity, physiological mechanisms, and reduction of chronic disease risk.[23,24] In addition, a study proposes that the consumption of bioactive components of *M. dubia* (camu-camu), such as the carotenoids, are associated with the prevention of cataracts, atherosclerosis, muscle atrophy, and multiple sclerosis.[25–27] Another study showed that the ascorbic acid found in the *M. dubia* (camu-camu) is a compound with an excellent reduction effect, making it an effective antioxidant.[28] Concerning the D-limonene cytotoxicity, Laughton et al. indicate that the *M. dubia* (camu-camu) compound is not toxic when it contacts the periapical area tissue.[29] Additionally, D-limonene has been studied by Pereira et al. in relation to colorectal cancer. He reported that the compound causes apoptosis (through the mitochondrial pathway) and affects the phosphatidylinositol 3—kinase/protein kinase B signaling pathway (survival and apoptosis).[30] Therefore, using essential oils is not only non-harmful to the periapical tissue but can provide additional health benefits.

The D-limonene compound causes the dissolution of high-impact polystyrene filaments (polystyrene).[31] For this reason, the *M. dubia* (camu-camu) can act as a solvent and have a softening function on the thermoplastic material. Additionally, it has also been investigated that volatile components, such as α-Pinene and D-limonene, may increase the dissolution action. These components are considered to be nontoxic hydrophilic solvent solutions that are widely used for ecological purposes as biodegradable components.[14] The solvent action, according to Dogan et al., acts in the gutta-percha through chemical means by breaking up the carbon covalent double bonds in the thermoplastic material and physically allowing the change of the gutta-percha from the thermoplastic state to liquid.[32]

The solubility of a substance in a solvent is due to the specific interactions between them. The main interaction forces are orientation forces, forces induced between dipolar and nonpolar molecules, dispersion forces, hydrogen bonding forces, and transfer forces. Because the *M. dubia* (camu-camu) oil has the D-limonene compound (considered a hydrocarbon), it meets different interaction forces. For example, dispersion forces, inductive forces, and hydrogen bonds.[32,33]

This study evidenced that the *M. dubia* (camu-camu) essential oil had a penetration force of 14.02 N and is an effective solvent in root canal re-treatment procedures. *In vitro* studies are not able to duplicate the exact situation as an *in vivo* scenario; the results of the study should be interpreted with caution given the limitations, and according to research on the application of solvents, it is reported that the use of solvents may fill accessories and/or lateral canals and cause inadequate sealing.[33] Furthermore, future studies must be conducted on Amazonian fruits containing the D-limonene compound to contribute to the field of endodontics.

Conclusion

We found that *M. dubia* oil (camu-camu) is an effective solvent in root canal re-treatment procedures. The penetration force recorded was lower than distilled water, xylene, orange peel oil, and eucalyptus oil. This means that it softens more gutta-percha than the other solvents tested.

Clinical Significance

The efficacy of the *M. dubia* (camu-camu) essential oil is relevant as it is a non-harmful solvent that would not harm the periapical tissue. Additionally, it would reduce the time of endodontic re-treatments procedures, which is beneficial for patients.

References

1. Siqueira JF Jr. Aetiology of root canal treatment failure: why well-treated teeth can fail. Int Endod J 2001;34(1):1–10. DOI: 10.1046/j.1365-2591.2001.00396.x
2. Jiao Y, Niu T, Liu H, et al. Protection against HEMA-induced mitochondrial injury *In Vitro* by Nrf2 activation. Oxid Med Cell Longev 2019;2019:3501059. DOI: 10.1155/2019/3501059
3. de Cristofaro Almeida G, Aun DP, Resende PD, et al. Comparative analysis of torque and apical force to assess the cutting behaviour of ProTaper Next and ProTaper Universal endodontic instruments. Aust Endod J 2020;46(1):52–59. DOI: 10.1111/aej.12351
4. Ahluwalia Y, Sharma U, Kumar N, et al. Adaptation of Single-Cone Gutta-Percha in Curved Canals Prepared and Obturated with Protaper and Heroshaper Systems by Using Cone Beam Computed Tomography. J Int Soc Prev Community Dent 2019;9(2):185–193. DOI: 10.4103/jispcd.JISPCD_398_18
5. Mello FW, Miguel AFP, Ribeiro DM, et al. The influence of apical extent of root canal obturation on endodontic therapy outcome: a systematic review. Clin Oral Investig 2019;23(5):2005–2019. DOI: 10.1007/s00784-019-02897-x
6. Safai P, Farzaneh B, Fekrazad R. The effects of pressure in vitro on three methods of root canal obturation. Diving Hyperb Med 2019;49(1):16–20. DOI: 10.28920/dhm49.1.16-20
7. Magalhães BS, Johann JE, Lund RG, et al. Dissolving efficacy of some organic solvents on gutta-percha. Braz Oral Res 2007;21(4):303–307. DOI: 10.1590/s1806-83242007000400004
8. Mckee RH, Adenuga MD, Carrillo JC. Characterization of the toxicological hazards of hydrocarbon solvents. Crit Rev Toxicol 2015;45(4):273–365. DOI: 10.3109/10408444.2015.1016216
9. Tang X, Wu W, Zeng W, et al. Copper-catalyzed oxidative carbon-carbon and/or carbon-heteroatom bond formation with O2 or internal oxidants. Acc Chem Res 2018;51(5):1092–1105. DOI: 10.1021/acs.accounts.7b00611
10. Jantarat J, Malhotra W, Sutimuntanakul S. Efficacy of grapefruit, tangerine, lime, and lemon oils as solvents for softening gutta-percha in root canal retreatment procedures. J Investig Clin Dent 2013;4(1):60–63. DOI: 10.1111/j.2041-1626.2012.00143.x
11. Yadav HK, Yadav RK, Chandra A, et al. The effectiveness of eucalyptus oil, orange oil, and xylene in dissolving different endodontic sealers. J Conserv Dent 2016;19(4):332–337. DOI: 10.4103/0972-0707.186447
12. Šmíd J, Kalousová M, Mandák B, et al. Morphological and genetic diversity of camu-camu [Myrciaria dubia (Kunth) McVaugh] in the Peruvian Amazon. PLoS One 2017;12(6):e0179886. DOI: 10.1371/journal.pone.0179886
13. Cunha-Santos ECE, Viganó J, Neves DA, et al. Vitamin C in camu-camu [Myrciaria dubia (H.B.K.) McVaugh]: evaluation of extraction and analytical methods. Food Res Int 2019;115:160–166. DOI: 10.1016/j.foodres.2018.08.031
14. Azevedo L, de Araujo Ribeiro PF, de Carvalho Oliveira JA, et al. Camu-camu (Myrciaria dubia) from commercial cultivation has higher levels of bioactive compounds than native cultivation (Amazon Forest) and presents antimutagenic effects in vivo. J Sci Food Agric 2019;99(2):624–631. DOI: 10.1002/jsfa.9224
15. Serrano A, Ros G, Nieto G. Bioactive compounds and extracts from traditional herbs and their potential anti-inflammatory health effects. Medicines (Basel) 2018;5(3):76. DOI: 10.3390/medicines5030076
16. Agrawal P, Ramanna PK, Arora S, et al. Evaluation of efficacy of different instrumentation for removal of gutta-percha and sealers in endodontic retreatment: an *in vitro* study. J Contemp Dent Pract 2019;20(11):1269–1273. DOI: 10.5005/jp-journals-10024-2670
17. Galiana M, Gualdoni M, Lugo C, et al. Review removal of gutta-percha with hand files, xylol and Reciproc. Odontoestomatología 2018;10(32):12–23. DOI: 10.22592/ode2018n32a3
18. Vadachkoria O, Mamaladze M, Jalabadze N, et al. Evaluation of three obturation techniques in the apical part of root canal. Georgian Med News 2019;(292–293):17–21. PMID: 31560656.
19. Donnermeyer D, Schäfer E, Bürklein S. Real-time intracanal temperature measurement during different obturation techniques. J Endod 2018;44(12):1832–1836. DOI: 10.1016/j.joen.2018.08.013
20. Faria-Júnior NB, Loiola LE, Guerreiro-Tanomaru JM, et al. Effectiveness of three solvents and two associations of solvents on gutta-percha and resilon. Braz Dent J 2011;22(1):41–44. DOI: 10.1590/s0103-64402011000100007
21. Das S, De Ida A, Das S, et al. Comparative evaluation of three different rotary instrumentation systems for removal of gutta-percha from root canal during endodontic retreatment: an *in vitro* study. J Conserv Dent 2017;20(5):311–316. DOI: 10.4103/JCD.JCD_132_17
22. Oyama KO, Siqueira EL, Santos Md. In vitro study of effect of solvent on root canal retreatment. Braz Dent J 2002;13(3):208–211. DOI: 10.1590/s0103-64402002000300014
23. Chang SK, Alasalvar C, Shahidi F. Superfruits: phytochemicals, antioxidant efficacies, and health effects - a comprehensive review. Crit Rev Food Sci Nutr 2019;59(10):1580–1604. DOI: 10.1080/10408398.2017.1422111
24. de Macêdo IYL, Garcia LF, Oliveira Neto JR, et al. Electroanalytical tools for antioxidant evaluation of red fruits dry extracts. Food Chem 2017;217:326–331. DOI: 10.1016/j.foodchem.2016.08.082
25. Simioni C, Zauli G, Martelli AM, et al. Oxidative stress: role of physical exercise and antioxidant nutraceuticals in adulthood and aging. Oncotarget 2018;9(24):17181–17198. DOI: 10.18632/oncotarget.24729
26. Inoue T, Komoda H, Uchida T, et al. Tropical fruit camu-camu (Myrciaria dubia) has anti-oxidative and anti-inflammatory properties. J Cardiol 2008;52(2):127–132. DOI: 10.1016/j.jjcc.2008.06.004
27. Quispe YN, Hwang SH, Wang Z, et al. Screening of Peruvian medicinal plants for tyrosinase inhibitory properties: identification of tyrosinase inhibitors in Hypericum laricifolium Juss. Molecules 2017;22(3):402. DOI: 10.3390/molecules22030402
28. Niki E. Interaction of ascorbate and alpha-tocopherol. Ann N Y Acad Sci 1987;498:186–199. DOI: 10.1111/j.1749-6632.1987.tb23761.x
29. Laughton MJ, Halliwell B, Evans PJ, et al. Antioxidant and pro-oxidant actions of the plant phenolics quercetin, gossypol and myricetin. Effects on lipid peroxidation, hydroxyl radical generation and bleomycin-dependent damage to DNA. Biochem Pharmacol 1989;38(17):2859–2865. DOI: 10.1016/0006-2952(89)90442-5
30. Pereira CV, Silva JM, Rodrigues L, et al. Unveil the anticancer potential of limomene based therapeutic deep eutectic solvents. Sci Rep 2019;9(1):14926. DOI: 10.1038/s41598-019-51472-7
31. Nardini M, Garaguso I. Characterization of bioactive compounds and antioxidant activity of fruit beers. Food Chem 2020;305:125437. DOI: 10.1016/j.foodchem.2019.125437
32. Dogan G, Kara N, Bagci E, et al. Chemical composition and biological activities of leaf and fruit essential oils from Eucalyptus camaldulensis. Z Naturforsch C J Biosci 2017;72(11-12):483–489. DOI: 10.1515/znc-2016-0033
33. Clark JH, Farmer TJ, Hunt AJ, et al. Opportunities for bio-based solvents created as petrochemical and fuel products transition towards renewable resources. Int J Mol Sci 2015;16(8):17101–17159. DOI: 10.3390/ijms160817101